

Remarks

Claims 58-87 were pending in the subject application. Submitted herewith is a Request for Continued Examination (RCE) under 37 CFR §1.114 for the subject application. Applicants are requesting a 3-month suspension of action, as indicated on the attached RCE. By this Amendment, claims 58, 60-64, and 68 have been amended, claim 59 has been cancelled, and new claim 88 has been added. Support for the new claim and amendments can be found throughout the subject specification including, for example, at page 45, lines 20-21, and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 58 and 60-88 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The Examiner indicates that the subject application does not comply with the drawings requirements. Submitted herewith are replacement drawings for Figures 4B, 6, 7A, 7B, 8A, and 8B, wherein the text size has been increased to 12pt. font. Entry and consideration of the replacement drawings is respectfully requested. Accordingly, withdrawal of the objection to the drawings is respectfully requested.

Claims 58-87 are rejected under 35 USC §112, first paragraph, as non-enabled by the subject specification. Under this rejection, the Examiner asserts that the claimed sequencing method is not enabled for the full scope of the claims. Applicants respectfully assert that the claimed invention is enabled by the subject specification. In order to meet the enablement requirement under 35 USC §112, first paragraph, a specification must describe how to make and how to use the claimed invention such that a person of ordinary skill in the relevant art would be able to practice the invention without resort to undue experimentation. *In re Glass*, 181 USPQ 31 (CCPA 1974). Applicants also respectfully submit that a significant amount of experimentation can be permitted under the enablement requirement. *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. & Int. 1982) (“The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine . . .”) (emphasis added).

By this Amendment, Applicants have amended independent claim 58 to recite that the labeled nucleotide comprises a quencher moiety and that the quencher moiety is removed from the

nucleotide once the nucleotide is incorporated into the extended primer. Applicants respectfully assert that the claimed method is enabled by the subject specification. The use of the quencher moiety provides for sequencing in the presence of labeled nucleotides and without the use of other steps, such as wash steps. The Examiner indicated in the Office Action that the method was not enabled for sequencing where all labeled nucleotides were present.

Under this rejection, the Examiner asserts that the quantity of experimentation necessary to practice the claimed method is “great” and “on the order of several man years” and “with little if any reasonable expectation of successfully enabling the full scope of the claims.” The Examiner also asserts that the amount of guidance provided by the subject specification is “limited.” Applicants respectfully disagree and assert that the quantity of experimentation is minimal and routine in the art, and that the subject specification provides sufficient guidance for practicing the claimed method. Applicants note that the ordinarily skilled artisan, having the benefit of the teachings of the subject specification, can practice the claimed invention. The steps of the method are straightforward and the subject specification provides substantial and explicit guidance for practicing the claimed method (see, for example, pages 21-24 of the subject specification). Accordingly, Applicants respectfully assert that there is sufficient detail and disclosure in the application to enable a person of ordinary skill in the art to carry out the invention without recourse to undue experimentation.

At page 8 of the Office Action, the Examiner asserts that the specification has not set forth reaction conditions under which each of the specified/claimed reagents are to be used in the claimed method. Applicants respectfully maintain that conditions for reactions utilizing nucleotides labeled with relevant moieties (*e.g.*, Fluorescein, Texas Red, Cy3 and Cy5 (cyanine)) are provided in the subject specification. For example, the third paragraph on page 73 of the specification describes using a thermostable polymerase. Although reaction conditions for every single dye or dye group set forth in claims 61, 62, and 67 are not provided, appropriate conditions would be readily apparent to the ordinarily skilled artisan and can be extended to the other dyes listed in the claims and are applicable regardless of whether the moiety functions as a fluorescence emitter or as a quencher. Applicants note that page 24, first paragraph, of the subject specification describes one specific emitter-quencher pair as fluorescein and Dabcyl. Another specific nucleotide that is described on page 24 of the subject specification is Pyrrolo-dCTP-dabcyl which is stated in the specification to be

incorporated by thermostable polymerases (examples of reaction conditions are provided on page 73 of the specification). At the time of the subject invention, and as stated in the specification, Internally Quenched Nucleotide fluorescent reporters (such as Pyrrolo-dCTP-dabcyl) were described in PCT publication WO 03/089670 (referenced in the subject specification) and are commercially available for real-time PCR, microarray technologies, and diagnostics from Lawler Scientific/Glen Research (Sterling, VA). The person of ordinary skill in the art would have been able to prepare and/or purchase these reagents and use them (in the claimed methods) according to conditions known in the art and/or the vendor recommended reaction conditions, without undue experimentation.

At page 10 of the Office Action, the Examiner asserts that the specification teaches (at page 11, lines 1-2) that sequencing will involve the use of extraordinary long linkers but that the claims do not require linkers of any particular length. Applicants respectfully assert that the use of linkers as discussed at page 11 of the subject specification applies to specific embodiments of sequencing methods, and in particular to those methods where the label is not cleaved from the nucleotide after incorporation. In Applicants' claimed invention, the label is cleaved from the incorporated nucleotide. Therefore, Applicants respectfully maintain that the section of the specification referred by the Examiner is not of particular relevance to the claimed invention, and the enablement thereof.

At the bottom of page 10 of the Office Action, the Examiner asserts that because the claim encompasses a method where all labeled nucleotides are present, then "one would not be able to readily determine which, if any, nucleotide(s) had been incorporated" and, thus, the claimed method is inoperable. Applicants respectfully assert that the method is enabled and operable. The subject specification describes ways in which the method can be practiced in the presence of labeled nucleotides. Applicants further note that claim 58 has been amended to recite the presence of a quencher moiety on the labeled nucleotide. This provides for sequencing where labeled nucleotides are present because the label is quenched until the nucleotide is incorporated into the extended primer and the quencher is removed.

Applicants also note that the references cited in previous responses were submitted to show the knowledge of a person of ordinary skill in the art and do not pertain to essential matter to be incorporated by reference. Thus, these references should be considered in that regard and not considered as essential matter that must be incorporated into the subject application.

The Examiner also discounts the *Mir et al.* publication provided by Applicants, indicating that it does not establish the state of the art at the time of filing of the subject application. Applicants respectfully assert that *Mir et al.* was submitted as evidence to show how sequencing could be performed without specific devices for temperature or fluid control. The *Mir et al.* publication showed that work could be done manually and without automation or specific new devices. Thus, the *Mir et al.* publication was cited to rebut the Examiner's assertions regarding devices for temperature and fluid control during the sequencing method; the *Mir et al.* publication shows that temperature and fluid control can be dealt with manually and without specific devices.

It is well settled in patent law that a specification is not required to teach that which is well known in the art. *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). Furthermore, as the Examiner is aware, every aspect of a generic claim need not have been carried out by an inventor, or exemplified in the specification, and only a reasonable amount of detail must be provided in order to enable members of the public to understand and carry out the invention. *Brenner v. Manson*, 148 USPQ 689 (1966). Applicants respectfully assert that the subject specification provides sufficient disclosure and sufficient detail for an ordinarily skilled artisan to make and use the full scope of the claimed method. In view of the above remarks, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Request for Continued Examination  
Figures 1-11 (13 total sheets)